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EPIDEMIOLOGY AND ECOLOGY OF THE CALIFORNIA SEROGROUP VIRUSES

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Abstract. The California serogroup viruses are important human pathogens, originally discovered in the United States, but now recognized to occur and cause disease in many parts of the world. In addition to their significance to public health, study of their natural history has resulted in a better understanding of the way in which arboviruses are maintained in nature. Viruses of the California serogroup have also been carefully investigated on the molecular level, resulting in a better appreciation of how viruses are constructed, organized, and replicate. William C. Reeves, in whose honor this symposium is held, has contributed throughout his career to each of these fields of endeavor. His pioneering work on these viruses, beginning with the discovery of the prototype California encephalitis virus, has helped to establish the foundations upon which our current understanding of these viruses is built.

Like many of the topics discussed in this symposium, the work of Bill Reeves impacts greatly on our current understanding of the California serogroup viruses. In fact, the history of these viruses begins with the original isolation of California encephalitis (CE) virus from *Aedes melanimon* mosquitoes captured in Kern County, California, in 1943 by Hammon and Reeves.[1,2] In 1945, the isolate, frequently referred to as BFS-283, was serologically linked to 3 cases of human encephalitis among hospitalized patients.[3] Although subsequent studies failed to identify additional cases of encephalitis in California due to this virus, strain BFS-283 did become a reference reagent for diagnostic testing and for identification of new virus isolates. In my presentation, I hope to show how Bill's original isolation has led to significant advances in several different disciplines of arbovirology, including recognition of the California serogroup viruses as important human pathogens worldwide, their use as models for a better understanding of disease ecology and maintenance in nature, and how the study of these viruses has provided critical links to our understanding of the molecular characteristics of viruses in the family Bunyaviridae.

California serogroup viruses as important human pathogens

When prototype CE virus was isolated, investigations of human illness in Kern County provided convincing evidence that encephalitis in 2 children, an infant and a 7-year-old, was due to infection with CE virus, and equivocal evidence was found for an additional case in an adult. At the time, the neutralizing antibody prevalence rate in humans in Kern County was about 11% (21 positive of 188 tested), a rate which increased with age and length of time of residency in the county. However, after the original isolations of the mid-1940s, additional human cases were not confirmed, even though routine testing for CE virus was performed on most reported cases compatible with CE virus infection.

The next evidence that California serogroup viruses were the cause of human disease came from a study in Florida, when Quick and colleagues[4] reported a human case. Unfortunately the specific strain causing infection was never determined. Following this report, Thompson and colleagues[5] isolated a California serogroup virus, which was antigenically distinct from the BFS-283 strain of CE virus, from the brain of a Minnesota child who had died in 1960 in a La Crosse, Wisconsin, hospital. This virus became known as La Crosse (LAC) virus, and is now recognized as one of the most important arbovirus pathogens found in the United States. Since 1955, the Centers for Disease Control have recorded the number of reported human encephalitis cases occurring annually nationwide. As shown in Figure 1, the first cases due to California serogroup virus infection were reported

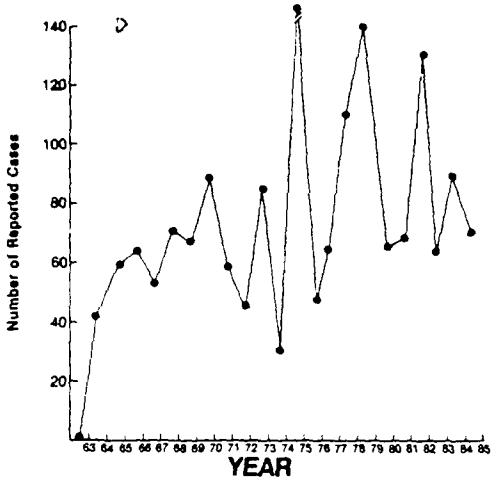

FIGURE 1. Number of encephalitis cases due to California serogroup virus infections reported by year, United States, 1963–1985 (from Kappus et al.[6] and T. P. Monath, CDC, Ft. Collins, personal communication).

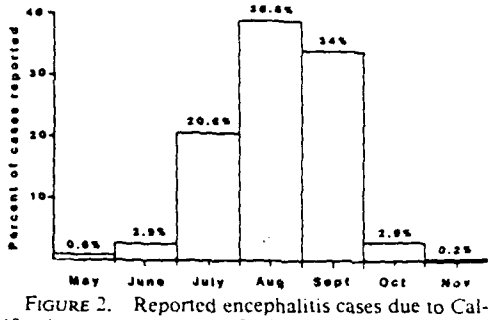

FIGURE 2. Reported encephalitis cases due to California serogroup virus infections by month of onset, United States, 1972–1981 (n = 806; from Kappus et al.[6]).

in 1963. The number of cases reported annually has rapidly increased, so that LAC virus encephalitis is now recognized as an important human disease, with an average of nearly 80 cases annually, and periodic annual peaks of well over 100 reported cases.[6] Please note that the cases depicted here are only those which meet the strict definition of encephalitis, and do not include those patients suffering only febrile disease without encephalitis. Consequently, these figures represent only a small fraction of the total disease burden due to California serogroup virus infections. Figure 2 shows that cases of encephalitis due to the California serogroup virus infections are highly seasonal in the United States, with virtually all cases occurring during the summer months. First cases are usually reported in May or June, but over 90% of reported cases occur in July, August, and September.

The distribution of reported encephalitis cases due to California serogroup viruses is shown in Figure 3 by state of occurrence, which clearly identifies the upper midwest region of the United States as highly endemic. Of almost 1,700 cases reported, more than 90% occurred in only 6 states: Ohio, Wisconsin, Minnesota, Illinois, Indiana, and Iowa. In all, 23 states have reported human California serogroup virus infections. Table 1 provides a summary of the number of cases reported by state, and each state's relative rank in terms of cases reported.

Antibody prevalence rates to California serogroup viruses reach 30% to 35% among persons residing or working in enzootic areas.[7] Monath and associates[7] estimated the annual incidence rate of infection to be about 2% for residents in rural areas, while those living in urban areas of the endemic zone have a rate of about 1%. The ratio of inapparent to apparent cases has not been determined; however, Kappus and colleagues[6] estimated from Monath and associates' Minnesota data[7] that an inapparent to apparent infection rate of approximately 26 to 1 existed in the clinically susceptible age group of birth to 15 years old. Since these data are based only on reported encephalitis cases, using in most cases LAC virus as the diagnostic antigen, they almost certainly under represent the true impact of California serogroup viruses as human pathogens.

Recently other California serogroup viruses also have been identified as responsible for human disease. The most significant of these appears to be Jamestown Canyon (JC) virus. This virus was originally isolated from *Culiseta inornata* mosquitoes captured in Colorado.[8] A similar or identical virus was also isolated from *Cs. inornata* by Bill Reeves and his colleagues in California in 1963 and named Jerry Slough (JS) virus.[8] JC and JS viruses are now thought to be synonymous, with the name Jamestown Canyon having priority.

The first evidence that JC virus was responsible for human disease came from a report describing a mild febrile illness which occurred among young men working in a forest camp in northern Wisconsin (Thompson, personal communication quoted in Sudia et al.[9]). More con-

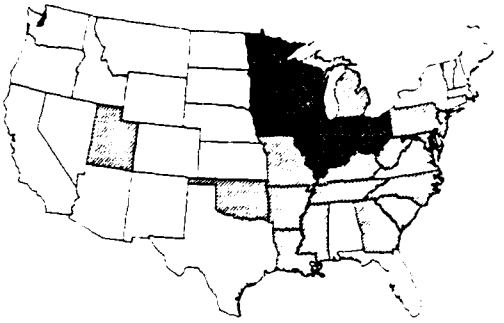

FIGURE 3. Reported cases of encephalitis due to California serogroups virus infections by state, United States, 1963–1985 (solid state, ≥50 cases reported; cross hatched states, <50 cases reported; blank state, no cases reported).

vincing evidence has been provided from a series of studies by Grimstad and his colleagues.[10] In 1982, they reported the first case of human encephalitis due to JC virus, which was diagnosed in an 8-year-old girl residing in rural southwestern Michigan. Deibel and associates[11] identified 10 additional clinical cases of JC virus infections in residents of New York, and 1 in Ontario, Canada. In a recent summary, Grimstad et al.[12] report on additional human cases of JC virus infections in Ohio and Wisconsin, and describe a serosurvey of Michigan residents in which they found 27.7% of 780 sera positive for neutralizing antibody to JC virus. The mean age of JC virus patients is 35 years old, while the mean age of LAC encephalitis patients is 7 to 8 years old. These results suggest that JC virus may be an important human pathogen affecting adults rather than children. JC virus is widespread throughout much of the United States, and clearly much more information is required before we fully understand the public health impact of this virus.

Snowshoe Hare (SSH) and trivittatus (TVT) viruses are 2 other members of the California serogroup suspected of causing human disease. Monath et al.[7] presented limited evidence suggesting that TVT virus was responsible for human disease in Minnesota, while Fauvel and colleagues[13] found evidence that SSH virus caused human infection in Canada. Little additional work has been reported since these initial observations; consequently, the impact of these viruses is not fully understood.

California serogroup viruses are not limited to the United States. In fact, members of the group have been found nearly worldwide. In Europe,

TABLE 1

*Reported cases of encephalitis due to California serogroup viruses by state, United States, 1963–1985**

Rank	State	Number of cases	Cumulative %
1	Ohio	574 (33.8%)	33.8
2	Wisconsin	394 (23.2%)	57.0
3	Minnesota	257 (15.1%)	72.1
4	Illinois	133 (7.8%)	79.9
5	Indiana	93 (5.4%)	85.3
6	Iowa	90 (5.3%)	90.6
7	New York	40 (2.4%)	93.0
8	North Carolina	28 (1.6%)	94.6
9	Michigan	14 (0.8%)	95.4
10	West Virginia	13 (0.8%)	96.2
11	Louisiana	12 (0.7%)	96.9
	Missouri	12 (0.7%)	97.6
13	Georgia	10 (0.6%)	98.2
14	Arkansas	5 (0.3%)	98.5
	Pennsylvania	5 (0.3%)	98.8
16	Kentucky	4 (0.2%)	99.0
	Tennessee	4 (0.2%)	99.2
18	New Jersey	3 (0.2%)	99.4
19	South Carolina	2 (0.1%)	99.6
	Utah	2 (0.1%)	99.7
21	Maryland	1 (0.1%)	99.8
	Mississippi	1 (0.1%)	99.9
	Oklahoma	1 (0.1%)	100.0
	Total	1,699	

* From Kappus et al.[9] and T. P. Monath, CDC, Fort Collins, personal communication.

Tahyna (TAH) virus is recognized as an important human pathogen in Czechoslovakia, where infection leads to a variety of different clinical presentations.[14–16] Another virus antigenically similar or identical to TAH virus, Lumbo virus, has been recorded in Africa, but its ability to cause human disease is not known.[17] In Scandinavia, Inkoo (INK) virus is known to cause a febrile disease in children.[18] The neutralizing antibody prevalence rate to INK virus throughout Finland is 24%, but it reaches 99% in some isolated populations.[19,20]

Three California serogroup viruses are recognized in Latin America: Guaroa (GRO), Melao (MEL), and Serra do Navio (SN) viruses. GRO virus has been isolated from persons suffering from a febrile disease, as well as from asymptomatic individuals.[21] Overt disease has not been associated with human infection by either MEL or SN virus, although human serosurveys have found antibody to these viruses.[18,22]

Finally, recent studies by the Chinese suggest that California serogroup viruses may be present in China as well. A serosurvey of persons residing in a suburb of Shanghai found 5 of 126 sera tested

TABLE 2

*Summary of California serogroup viruses of the world: Original sources, localities, and year of first isolation**

Virus	Abbreviation	Originally isolated from	Locality of isolation	Year of isolation
California encephalitis	CE	*Ae. melanimon*	California, USA	1943
Trivittatus	TVT	*Ae. trivittatus*	North Dakota, USA	1948
Guaroa	GRO	Human	Guaroa, Colombia	1956
Tahyna (= Lumbo)	TAH	*Ae. caspius*	Czechoslovakia	1958
	LUM	*Ae. pembaensis*	Mozambique	1959
Snowshoe Hare	SSH	*Lepus americanus*	Montana, USA	1958
Melao	MEL	*Ae. scapularis*	Trinidad	1955
San Angelo	SA	*An. p. pseudopunctipennis*	Texas, USA	1958
La Crosse	LAC	Human	Wisconsin, USA	1960
Keystone	KEY	*Ae. atlanticus-tormentor*	Florida, USA	1964
Jamestown Canyon (= Jerry Slough)	JC	*Cs. inornata*	Colorado, USA	1961
	JS	*Cs. inornata*	California, USA	1963
Inkoo	INK	*Ae. communis/punctor*	Finland	1964
Serra do Navio	SN	*Ae. fulvus*	Amapa, Brazil	1966

* Bocus virus, originally considered to be a member of the California serogroup, is a strain of mouse hepatitis virus.

with antibody to SSH virus.[23] Neutralization tests with CE (BFS-283), SSH, MEL, TAH, and TVT viruses gave the highest titers to SSH virus. While it is not clear at present whether disease is associated with infection, it is apparent that at least 1 California serogroup virus is present in China.

Twelve viruses now comprise the group, and evidence of human infection has been obtained for each virus, with the exception of San Angelo virus (Tables 2, 3). In addition, 8 California serogroup viruses have been associated with human disease (Table 3).

Review of the human disease due to California serogroup viruses as now recognized, both in the United States and abroad, attests to the significance of Bill's original work on this group. The isolation of BFS-283, the prototype CE virus, and the early association of this virus as a cause of human disease, led to both the discovery of an entire group of antigenically related viruses, and to the recognition that these viruses are important human pathogens. Clearly the impact of these viruses on human health requires further study; thus the fruits of Bill's original discoveries will continue to serve as the basis for epidemiological investigations for years to come.

Investigations of California serogroup viruses as models for mosquito-borne virus disease ecology

Aedes triseriatus *and La Crosse virus.* Following recognition of the public health importance of LAC virus, intense investigations were begun to determine how this virus is maintained in nature. These studies were led by scientists at the University of Wisconsin, including Wayne Thompson, Gene DeFoliart, Tom Yuill, and an especially gifted group of graduate students. Their initial finding was the identification of a strong association between *Ae. triseriatus* mosquitoes and LAC virus.

Subsequently, Watts and colleagues[24] demonstrated that *Ae. triseriatus* mosquitoes could vertically transmit the virus, from an infected female to her progeny, by transovarial transmission. Next, Thompson and Beaty[25] demonstrated that infected male mosquitoes could infect uninfected females during mating, thus demonstrating a heretofore unrecognized means of horizontal transmission of arboviruses. Additional

TABLE 3

California serogroup viruses as causes of human disease

Virus	Antibody in humans	Clinical disease
California encephalitis	Yes	Yes
La Crosse	Yes	Yes
Jamestown Canyon (Jerry Slough)	Yes	Yes
Snowshoe Hare	Yes	Yes
Trivittatus	Yes	Yes
Tahyna (Lumbo)	Yes	Yes
Inkoo	Yes	Yes
Guaroa	Yes	Yes
Keystone	Yes	No
Serra do Navio	Yes	No
Melao	Yes	No
San Angelo	No	No

studies identified those vertebrate species commonly infected in nature and their potential to produce a viremia of sufficient titer to infect feeding *Ae. triseriatus* mosquitoes, while others began to define the ecological habitats suitable for harboring *Ae. triseriatus* mosquitoes. Finally, enough information was obtained to generate a hypothetical transmission cycle for LAC virus in nature (see reviews by LeDuc,[26] Calisher and Thompson,[27] and Grimstad[28]). With this, it became obvious that the ecology of LAC virus, and indirectly that of the disease LAC encephalitis, was directly linked to the ecology of the mosquito vector, *Ae. triseriatus*.

Aedes atlanticus *and Keystone virus.* Coincidental with the studies of LAC virus in Wisconsin were studies by a group of U.S. Army scientists from the Walter Reed Army Institute of Research working on the Delaware-Maryland-Virginia (DelMarVa) Peninsula. This group was investigating the ecology of another California serogroup virus, Keystone (KEY) virus. As with LAC virus and *Ae. triseriatus*, a strong association was found between KEY virus and its primary mosquito vector, *Ae. atlanticus*. Further study revealed that KEY virus also was vertically transmitted from infected female to offspring.[29] Unlike *Ae. triseriatus*, *Ae. atlanticus* breeds in ground pools, and on the DelMarVa Peninsula, unusually heavy rainfall is required to flood the preferred breeding sites of this species.[30] Such rainfall is relatively infrequent, and usually is associated with late summer hurricanes; consequently, KEY virus is not continually transmitted, but rather transmission is initiated only after vertically infected mosquitoes emerge from their ground pool breeding sites. Studies with KEY virus are noteworthy both from the standpoint of confirming the importance of vertical transmission as a maintenance mechanism for California serogroup viruses, and also for demonstrating the potential importance of climatic conditions such as rainfall on transmission of these viruses.[31]

As many of you know, Bill played an important part in these studies as well, since I used much of the KEY virus work as part of my doctoral dissertation, and Bill served on my committee. One of his most significant contributions, in my mind, was his encouragement of my collaboration with Paul Fine, then working at Berkeley. Paul and I spent many hours, primarily at Bill's Bakersfield field station, talking about the quantitative aspects of KEY virus transmission. The ultimate product was a model which systematically identified and quantified the parameters involved in maintenance of this virus.[32] This study remains one of my favorites, since it attempts to look at the "big picture," and has in my opinion helped to establish the foundation for some additional applications of quantitative aspects of arbovirus ecology, as I will discuss later.

Recognition that vertical transmission was critical to the maintenance of both LAC and KEY viruses suggested the possible importance of this means of transmission for all California serogroup viruses. Subsequent studies have now demonstrated that most viruses of this group are indeed vertically transmitted by their primary vector mosquitoes.[26, 27] These observations also led to a reexamination of other mosquito-borne virus diseases to determine if they too are maintained through vertical transmission, as Leon Rosen will discuss later on in this symposium.

Demonstration that the ecology of vector mosquito species closely reflected the ecology of the viruses they transmitted, and thus indirectly the virus diseases themselves, led to investigation of ways to predict the presence or absence of vector populations by measurement of environmental markers critical to vector survival. One of the most successful demonstrations of this concept has been provided by Charlie Bailey and Ken Linthicum studying the phlebovirus, Rift Valley fever (RVF), in eastern and southern Africa. A strong association was identified by these investigators and others[33] between the occurrence of RVF virus infections in domestic animals, and years of heaviest rainfall, as shown in Figure 4.

Areas where outbreaks occurred also correlated with the presence of dambos, depressions in the African savannas which collect water following prolonged heavy rains, and serve as watering holes for both wildlife and domestic animals. Studies of the mosquito fauna associated with these dambos demonstrated that a portion of the mosquito population may be transovarially infected with RVF virus.[34] The requirement for exceptionally heavy rainfall to hatch these mosquitoes, and the unique physical characteristics of dambos, which allows them to be recognized through satellite imagery or aerial photography, provided 2 measurable parameters for potential use in remotely monitoring RFV virus activity. Specific dambos can be identified, thus allowing

very localized examination of mosquito breeding sites. Further, the amount of rainfall can be indirectly measured over a large area by satellite. Together, these measurements might allow investigators to predict outbreaks of RVF, even in remote areas where firsthand data collection may not be possible. Recent studies by Linthicum et al.[35] have in fact demonstrated that a past RVF epizootic could have been predicted through measurement of these parameters, thus demonstrating the potential utility of this concept.

In summary, studies on the California serogroup viruses indicated that vertical transmission was an important maintenance mechanism of these viruses. Further, investigations of these viruses led to recognition that through vertical transmission, the ecology of the principal vector species was intimately linked to the ecology of the virus itself, and thus to the resulting human disease. Finally, demonstration that the ecological requirements of important vector species could be identified and quantified, suggests that at least in theory, diseases maintained by those vector species might be remotely monitored and perhaps predicted. While these fundamental observations were based on studies of California serogroup viruses, the utility of these findings extends to any vector-borne disease where vertical transmission occurs and where the critical requirements for its maintenance in nature can be identified, quantified, and measured.

California serogroup viruses and molecular virology

I would like to close with a brief discussion of the influences that the California serogroup viruses have had on our current understanding of the molecular characteristics of viruses of the family Bunyaviridae. Several recent books and chapters have provided excellent overviews of the California serogroup viruses and their relative status within the family Bunyaviridae;[27, 36–38] however, I think that it is useful to mention 3 contributions which have helped to solidify our concepts regarding the development of this family. All of these contributions relied on California serogroup viruses as models for these now classic studies.

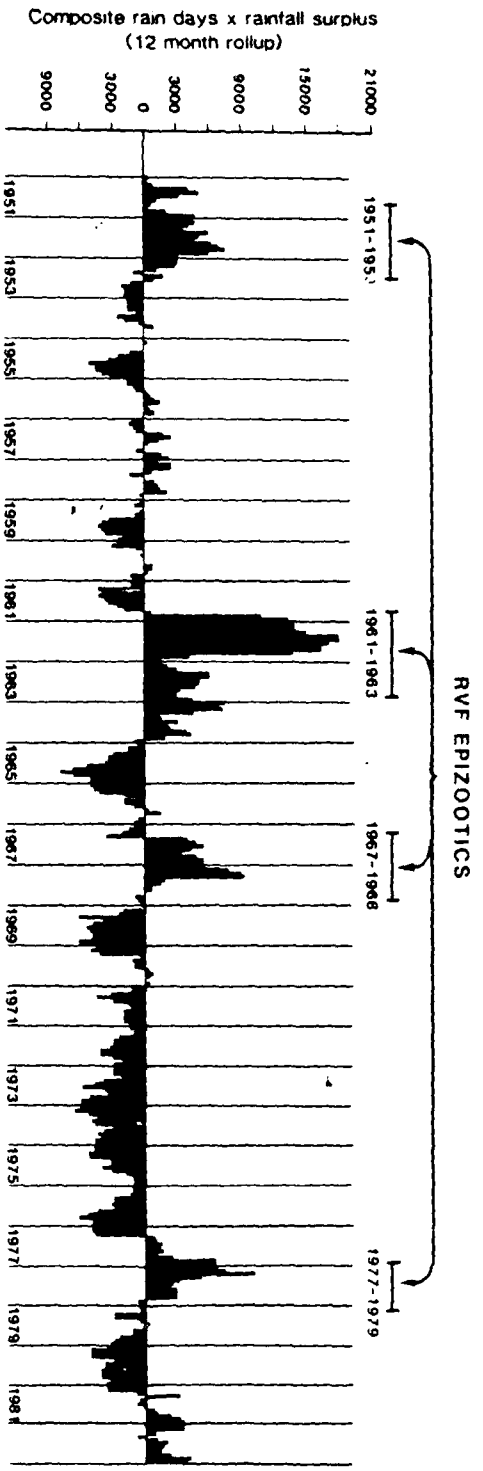

FIGURE 4. Relationship between Rift Valley fever epizootics and rainfall in Kenya, 1951–1982 (reproduced with permission of Davies et al.[33]).

As mentioned previously, Bill's original isolation of prototype CE virus, and his subsequent isolation of JS virus, were instrumental in recognition of what was to become the California serogroup viruses. In fact, Bill participated in the original discussions of the Subcommittee on the Immunological Relationships Among Catalogued Arboviruses (SIRACA) which led to the creation of the group. Membership in the California serogroup was based on the antigenic interrelationships of these viruses, and was worked out by Jordi Casals and his colleagues at the Rockefeller Foundation and the Yale Arbovirus Research Unit, and by Gladys Sather and Bill Hammon, then at the University of Pittsburgh.[39] During this era, Casals examined several new viruses isolated in the United States and in overseas research laboratories. By comparing the reactivity of each virus and its homologous antisera with those of other viruses, Casals provided the foundations for what became an antigenic classification of the arboviruses, an organizational framework which remains one of the primary tools of arbovirus classification today.

A second significant event in the development of the family Bunyaviridae was the work of Fred Murphy and his colleagues,[39, 40] who demonstrated that viruses of the Bunyamwera Supergroup, as viruses of the family Bunyaviridae were then known, shared ultrastructural similarities when examined under the electron microscope. Again, the California serogroup viruses were well represented in these classic studies.

These observations provided the background for subsequent biochemical analyses of these viruses. David Bishop and his colleagues[37, 42] were at the forefront in these investigations, and once again the California serogroup viruses played a prominent role. The California serogroup viruses were used to define the characteristic biochemical composition we now know to be descriptive of members of the virus family Bunyaviridae: 2 envelope glycoproteins, which together with lipid, surround internal nucleocapsids consisting of separate large, medium, and small RNA segments of negative polarity intimately associated with a nucleoprotein, and a large protein of putative transcriptase function. Detailed analysis of the RNAs has revealed that each RNA segment contains the same complementary sequences on their ends, and the conservation of these sequences parallels their antigenic relationships, which taken together form the basis for the description of separate genera.[37] I might add parenthetically that this information has recently played an important role in our efforts to classify the hantaviruses, now recognized as a new genus within the family Bunyaviridae.[43]

Early experiments suggested that closely related viruses with common characteristics could exchange RNA segments, resulting in stable reassortant viruses. These initial observations were extended by clearly demonstrating that reassortment can occur in dually infected mosquitoes, and that these reassortants can be transmitted.[37] Additional studies have determined that such reassortment occurs in nature as well, implying a role in the natural history and evolution of the bunyaviruses.

These observations, Casals' demonstration that viruses could be grouped by antigenic interrelatedness, Murphy's finding of similar morphology among antigenically related viruses of the Bunyamwera supergroup, and Bishop and colleagues' biochemical analyses, formed the foundations for the creation and organization of what is now known as the family Bunyaviridae. While it's a long way from Bill's original isolation of BFS-283, the origins of the family do indeed stem, at least in part, from Bill's early contributions.

The California serogroup viruses continue to play a vital role in furthering our understanding of the molecular characteristics of bunyaviruses. The current literature is replete with reports of monoclonal antibodies, cloning and expression of specific genes, and other applications of biotechnology to the study of these viruses, indicating that they continue to provide important models for the investigation of the molecular characteristics of arboviruses. As but one current example, let me call to your attention the recent publication of Barry Beaty's and Neal Nathanson's groups,[44] demonstrating that a G1 glycoprotein epitope of LAC virus functions as a determinant of infection for *Ae. triseriatus* mosquitoes. Central to the theme of this paper is the question of what determines the vector specificity of arboviruses, and more specifically, the interactions between virus and the midgut cells of vector mosquitoes. Clearly Bill and his colleagues at Berkeley have contributed extensively in this area, through their studies of western equine encephalitis virus and *Culex tarsalis* mosquitoes.

I have tried to follow the evolution of our un-

derstanding of the California serogroup viruses in three separate areas: as human pathogens, as models for vector-borne disease ecology, and as models for the study of the molecular biology of viruses of the family Bunyaviridae. These diverse fields all share a common ancestry, and a significant link in their origins, to Bill's original isolations and to his early efforts. None of us could have predicted back in the 1940s the impact that those observations would hold. Yet today, we all recognize the California serogroup viruses as important human pathogens, as prime examples of arbovirus ecology, and as vital links to our understanding of the molecular basis of virology. Bill has certainly left his mark on arbovirology through his work on the California serogroup viruses.

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